Guidance for Industry

Labeling OTC Human Drug Products

Updating Labeling in ANDAs

DRAFT GUIDANCE

Comments and suggestions regarding this guidance document may be submitted at any time. Submit comments to Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that published in the *Federal Register*.

For questions on the content of this guidance document, contact Gerald M. Rachanow, 301-827-2222 or (OGD) John Grace, 301-827-5845.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

February 2001
OTC

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Center for Drug Evaluation and Research
Food and Drug Administration
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TABLE OF CONTENTS

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Labeling OTC Human Drug Products — Updating Labeling in ANDAs

This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statutes and regulations.

If you plan to submit comments on this draft guidance, to expedite FDA review of your comments, please:

- *Clearly explain each issue/concern and, when appropriate, include a proposed revision and the rationale/justification for the proposed change.*
- *Identify specific comments by line number(s); use the PDF version of the document, if possible.*

I. INTRODUCTION

This guidance is intended to assist manufacturers, packers, and distributors of over-the-counter (OTC) drug products marketed under ANDAs (abbreviated new drug applications) and the manufacturer of the corresponding reference listed drug (RLD) implement the Agency's regulation on standardized content and format requirements for the labeling of OTC drug products. The guidance contains recommendations on how RLD and ANDA holders can update their labeling in a timely manner consistent with the regulation on OTC drug labeling (21 CFR 201.66).

II. BACKGROUND

In the *Federal Register* of March 17, 1999 (64 FR 13254), the Food and Drug Administration (FDA) published a final regulation establishing standardized content and format requirements for the labeling of OTC drug products. Standardized labeling for OTC

[1] This guidance has been prepared by the Division of Over-the-Counter Drug Products and the Office of Generic Drugs (OGD) in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration (FDA).

drug products is intended to make it easier for consumers to read and understand OTC drug product labeling and use such products safely and effectively.

The new labeling regulation in 21 CFR 201.66 covers all OTC drug and drug-cosmetic products, whether marketed under a new drug marketing application (NDA), abbreviated new drug application (ANDA), or OTC drug monograph (or product not yet the subject of a final OTC drug monograph). The implementation dates are the same for products that were legally marketed under an NDA or ANDA before the date of the final rule.

Section 201.66(c)(1) through (c)(9) of the labeling regulation provides the content requirements for labeling information, including information about active ingredients, their purpose, use, warnings, directions, other information, and inactive ingredients.

Questions have been submitted to the Agency asking whether products marketed under an ANDA can use the new labeling content and format requirements prior to the RLD, or must the ANDA holder wait for the RLD holder to submit revised labeling and then submit labeling that is the same as that of the RLD. These questions have been raised because under the Federal Food, Drug, and Cosmetic Act, a drug product marketed under an ANDA must bear the same labeling as that approved for the RLD (21 U.S.C. 355(j)(2)).

The "same labeling" requirement does not require an ANDA's labeling to be identical to that of the RLD. Among permissible differences, FDA regulations (21 CFR 314.94(a)(8)(iv)) allow an ANDA holder to include labeling that is different from that of the RLD where the ANDA labeling revisions are made "to comply with current FDA guidelines or other guidance." In this case, the new Drug Facts labeling changes to be made in ANDA labeling would result from a regulation (21 CFR 201.66). In addition, the preamble to the OTC drug product labeling final regulation states that the adoption of the new labeling format for most OTC drug products marketed under an NDA or ANDA *would be considered editorial or minor changes* and that the majority of the changes required by the final regulation could be submitted to the Agency in an annual report to the application under 21 CFR 314.70(d)(3).[2]

III. FDA RECOMMENDED LABELING EXAMPLES FOR SOME PRODUCTS

The Agency stated in its OTC drug product labeling final regulation that it expects 522 submissions (350 to NDAs and 172 to ANDAs) for labeling changes under 21 CFR 201.66(c) and (d). Submissions to NDA's will vary as many different products are marketed under NDAs. However, submissions to ANDAs will be concentrated in the following products:

[2] Changes to labeling that go beyond the interchangeable terms allowed in Agency regulations (i.e., in 21 CFR 330.1(i) or (j)) should be submitted to the Agency in a supplement for preapproval. Questions about the need to submit a labeling supplement for preapproval should be directed to the appropriate Agency division. See also CDER's guidance *Changes to an Approved NDA or ANDA* (November 1999) .

- ibuprofen tablets: 35 expected

More than 5 ANDA submissions are expected for the following:

- acetaminophen suppositories
- cimetidine tablets
- loperamide tablets and oral solution
- miconazole vaginal cream and suppositories
- minoxidil topical solution
- naproxen sodium tablets

Together, these constitute about 50 percent of all OTC drug product ANDAs. The Agency believes manufacturers of ANDA products ***need not wait*** to implement the new labeling format until after the RLD holder has submitted its labeling.

To facilitate the implementation of the new Drug Facts labeling for ANDA products, the Agency is developing labeling examples for manufacturers to follow for each of the products listed above. Manufacturers of OTC ANDA products for which FDA does not currently plan to develop labeling examples may implement labeling changes before their RLD's and may use these labeling examples to guide their own effort to comply with 21 CFR 201.66.

Two labeling examples, which show specific product labeling in the new format, are included in this draft guidance: One for ibuprofen 200 milligram (mg) in a tablet/capsule dosage form; and one for minoxidil topical solution 2% for men and women. These labeling examples may also be found on the OTC Internet website at www.fda.gov/cder/otc/. The agency intends to develop the additional labeling examples referenced above, and they, too, will be made available before the close of the comment period at the same OTC Internet website.

The labeling examples developed as part of this guidance represent the agency's current thinking on this subject, and they do not create or confer any rights for or on any person and do not operate to bind FDA or the public. An alternative approach may be used if such an approach satisfies the requirements of the applicable statutes and regulations.

When using the labeling examples, it should be noted that interchangeable terms can be used in certain places (see 21 CFR 330.1(i) and (j)). For example, although the Agency uses the word *doctor* in its labeling examples, the term *physician* can also be used where appropriate.

IV. SUBMISSION OF NEW LABELING IN AN ANNUAL REPORT

Manufacturers can submit their ANDA labeling changes in their annual reports according to 21 CFR 314.70(d)(3) and need not submit a supplemental application to the Agency for preapproval under several different circumstances:

- If they use the Agency's labeling examples to make their changes

- If they do not use the Agency's labeling examples, but change their labeling in accordance with 21 CFR 201.66 and 21 CFR 330.1(i) or (j)

- Where the Agency has not provided any labeling examples, if they change their labeling in accordance with 21 CFR 201.66 and 21 CFR 330.1(i) or (j)

Manufacturers should submit preapproval supplements to the NDA or ANDA, as appropriate, if they make changes to the content of the labeling or wording changes that go beyond those provided for in 21 CFR 330.1(i) or (j).

Example Drug Facts Label for Ibuprofen 200 mg in a Tablet/Capsule Dosage Form

Drug Facts

Active ingredient (in each [insert dosage unit]) ***Purposes***
Ibuprofen 200 mg.....Pain reliever/fever reducer

Uses
- temporarily relieves minor aches and pains due to:
  - headache
  - muscular aches
  - minor pain of arthritis
  - toothache
  - backache
  - the common cold
  - menstrual cramps
- temporarily reduces fever

Warnings
Allergy alert: Ibuprofen may cause a severe allergic reaction which may include:
- hives
- facial swelling
- asthma (wheezing)
- shock

Alcohol warning: If you consume 3 or more alcoholic drinks every day, ask your doctor whether you should take ibuprofen or other pain relievers/fever reducers. Ibuprofen may cause stomach bleeding.

Do not use if you have ever had an allergic reaction to any other pain reliever/fever reducer

Ask a doctor before use if you have
- stomach pain
- problems or serious side effects from taking pain relievers or fever reducers

Ask a doctor or pharmacist before use if you are
- under a doctor's care for any serious condition
- taking any other drug
- taking any other product that contains ibuprofen, or any other pain reliever/fever reducer

When using this product take with food or milk if stomach upset occurs

Stop use and ask a doctor if
- an allergic reaction occurs. Seek medical help right away.
- pain gets worse or lasts more than 10 days
- fever gets worse or lasts more than 3 days
- stomach pain or upset gets worse or lasts
- redness or swelling is present in the painful area
- any new symptoms appear

If pregnant or breast-feeding, ask a health professional before use. It is especially important not to use ibuprofen during the last 3 months of pregnancy unless definitely directed to do so by a doctor because it may cause problems in the unborn child or complications during delivery.
Keep out of reach of children. In case of overdose, get medical help or contact a Poison Control Center right away.

Directions[3]
- **do not take more than directed**
- adults and children 12 years and older:
  - take 1 [insert dosage unit] every 4 to 6 hours while symptoms persist
  - if pain or fever does not respond to 1 [insert dosage unit], 2 [insert dosage unit(s)] may be used
  - do not exceed 6 [insert dosage unit(s)] in 24 hours, unless directed by a doctor
  - the smallest effective dose should be used
- children under 12 years: ask a doctor

Other information
- optional - tamper evident statement
- store at 20-25^0 C (68-77^0 F). Avoid high humidity and excessive heat above 40^0 C (104^0 F).
- optional - see [end or side] panel for lot number and expiration date

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Inactive ingredients [list ingredients in alphabetical order]

Questions or comments? call toll free **1-800-XXX-XXXX**

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*NOTE: The **Drug Facts (continued)** title should appear wherever the labeling continues onto another panel of the package.*

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[3]The information for the two age groups can be presented in a table format in accord with 21 CFR 201.66(d)(9) with the "do not take more than directed" statement appearing above the top line of the table.

Example Drug Facts Label for Minoxidil Topical Solution 2% for Men and Women

Drug Facts

Active ingredient ***Purpose***
Minoxidil 2% w/v.....Hair regrowth treatment

Use
- to regrow hair on the scalp

Warnings
For external use only
Flammability warning: Keep away from fire or flame [Include if product meets the criteria in 16 CFR 1500.3(b)(10)]

Do not use if
- your degree of hair loss is more than that shown on the side of this carton. Minoxidil topical solution 2% may not work.
- you have no family history of hair loss
- hair loss is sudden and/or patchy

[Use for products for women]■ hair loss is associated with childbirth
- you do not know the reason for your hair loss
- you are under 18 years of age. Do not use on babies and children.
- scalp is red, inflamed, infected, irritated, or painful
- you use other topical prescription products on the scalp

When using this product
- do not apply on other parts of the body
- avoid contact with the eyes. In case of accidental contact, rinse eyes with large amounts of cool tap water.
- it takes time to regrow hair. You may need to use minoxidil topical solution daily for at least 4 months before you see results.
- the amount of hair regrowth is different for each person. Minoxidil topical solution will not work for everyone.

Stop use and ask a doctor if
- chest pain, rapid heart beat, faintness, or dizziness occurs
- sudden, unexplained weight gain occurs
- your hands or feet swell
- redness or irritation occurs.
- you do not see hair regrowth in [insert 12 for products for men and 8 for products for women] months

[Use for products for women] **If pregnant or breast feeding,** ask a health professional before use.
Keep out of reach of children. If swallowed, get medical help or contact a Poison Control Center right away.

Directions

- apply one mL 2 times a day directly onto the scalp in the hair loss area
- using more or more often will not improve results
- continued use is necessary to increase and keep your hair regrowth, or hair loss will begin again

Other information

- see hair loss pictures on side of this carton
- before use, read all information on carton and enclosed booklet
- keep the carton. It contains important information.
- [Use for products for men] in clinical studies of mostly white men aged 18-49 years with moderate degrees of hair loss, the following response to minoxidil topical solution 2% was reported: 26% of men reported moderate to dense hair regrowth after using minoxidil topical solution 2% for 4 months (26% had moderate to dense regrowth; 33% had minimal regrowth). This compares with 11% of men reporting hair regrowth after using the placebo, the liquid without minoxidil in it, for 4 months (11% had moderate to dense regrowth; 31% had minimal regrowth).
- [Use for products for women] in clinical studies of mostly white women aged 18-45 years with mild to moderate degrees of hair loss, the following response to minoxidil topical solution 2% was reported: 19% of women reported moderate hair regrowth after using minoxidil topical solution 2% for 8 months (19% had moderate regrowth; 40% had minimal regrowth). This compares with 7% of women reporting moderate hair regrowth after using the placebo, the liquid without minoxidil in it, for 8 months (7% had moderate regrowth; 33% had minimal regrowth).
- optional - storage conditions [that are appropriate for the product in both ^{0} C and ^{0} F]

Inactive ingredients [list ingredients in alphabetical order; list alcohol as % v/v]

Questions or comments? call toll free **1-800-XXX-XXXX**

*NOTE: The **Drug Facts (continued)** title should appear wherever the labeling continues onto another panel of the package.*